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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,760	09/27/2005	Anders Ljunggren	101026-1P US	3784

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
10/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,760	LJUNGGREN ET AL.	
	Examiner	Art Unit	
	Timothy P. Thomas	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-20* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/27/2005 and 11/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of specie (i), administration of an angiotensin II type I receptor antagonist alone; and (ia) candesartan cilesetil (the compound of general formula I wherein A is the I:5 moiety) as the an angiotensin II type I receptor antagonist specie and that claims 11-13 and 17-20 read on the elected species in the reply filed on 9/12/2007 is acknowledged. The traversal is on the ground(s) that the Examiner has not prima facie established the serious burden requirement. This is not found persuasive because the sections of the MPEP cited by applicant (in Chapter 800) are not applicable to applications filed under 35 U.S.C. 371 (see MPEP 801). The appropriate requirements are described in MPEP Chapter 1800. As pointed out on p.3, item # 4 of the restriction requirement of 7/30/2007, the technical feature common to the species has been taught in the prior art; and does not comprise a special technical feature. Therefore the species recited do not comprise a general inventive concept under PCT Rule 13.2 and the election of species requirement is maintained.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected specie, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/12/2007.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 11-13, 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use in claim 11 of the language "whereby" and "an angiotensin II type 1 receptor **alone** or in combination...is administered to a subject...", indicates closed claim structure, where the first option of the method consists of (not comprises) the administration of an angiotensin II type 1 receptor **alone**, i.e., "alone" may be construed to indicate administration without even the adjuvants, diluents and carriers mentioned on p. 7, lines 18-22 of the specification; an alternate view might be that "alone" is interpreted only with respect to active ingredient(s) administered. The second option of claim 11, likewise, could either be interpreted as consisting of the administration of one angiotensin II type 1 receptor and one metabolically neutral antihypertensive substance combined, without the option of other additional non-active ingredients (exactly two components are administered) vs. an alternate interpretation, where the language of the second option is construed as referring to the two active ingredients with the possibility of adjuvants, etc.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11-13 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating symptoms associated with metabolic syndrome and identifying an individual in need of such treatment, does not reasonably provide enablement for "prevention" of metabolic syndrome or identifying an individual in need of such a prevention therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

"Prevention" implies that a condition or disease will not develop. The etiology of metabolic syndrome is not well understood; some experts indicate that lifestyle modification, including diet and exercise, with a goal of weight reduction is a necessary foundation of any successful treatment regimen, and that pharmacological therapy should be individualized and targeted to symptoms of the condition in the individual. Therefore, applicant's claimed method, which focuses on administration of an angiotensin II type 1 receptor antagonist, either alone or in combination with a metabolically neutral antihypertensive substance, does not address the root causes (such as poor diet, sedentary lifestyle and weight gain, genetic or other unknown causes), or all of the different symptoms that may be present. Furthermore, applicant does not teach how to identify a patient in need of "prevention" therapy.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not

'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method for the treatment and/or "prevention" of metabolic syndrome, whereby a pharmaceutically and pharmacologically effective amount of an angiotensin II type 1 receptor antagonist, either alone or in combination with a metabolically neutral antihypertensive substance is administered to a subject in need of the treatment or prevention. Thus, the claims taken together with the specification imply that administration of any angiotensin II type 1 receptor antagonist, such as candesartan cilexetil or the administration of that angiotensin II type 1 receptor antagonist along with any metabolically neutral antihypertensive substance will prevent metabolic syndrome in a subject in need of prevention.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Stone, et al. ("Metabolic syndrome management"; Expert Opin. Pharmacother.; 2007; 8(13): 2059-2075) teaches that metabolic syndrome occurs in genetically susceptible individuals with environmental influences, and may be compounded by other metabolism disorders or pharmacological therapy that influences insulin resistance or promotes weight gain. Stone presents the opinion that treatment of

metabolic syndrome should focus on treatment of each individual component of the syndrome first and lifestyle modification, including diet and exercise with a goal of weight reduction as a foundation for any successful treatment regimen; that pharmacological therapy should be individualized and targeted to normalize blood pressure, HDL cholesterol, triglycerides and glucose values (abstract).

Pershadsingh (US 2007/0203213 A1) teaches that some angiotensin II type 1 receptor antagonists also function as activators of peroxisome proliferator activated receptors (PPAR), e.g., telmisartan and irbesartan, and these compounds are useful in the treatment of metabolic syndrome (abstract; paragraph 0016); however, the activation of PPAR does not occur for other angiotensin II type 1 receptor antagonists, including valsartan and eprosartan; but that similar effects in the treatment of diseases like metabolic syndrome can be obtained upon administration of the dual acting compounds or for administration of an angiotensin II type 1 receptor, such as candesartan cilexetil, valsartan or eprosartan, in combination with a known PPAR activator.

Mechanisms involved in genetic factors are not that well understood, there is variation in individual symptoms associated with metabolic syndrome that must be individually addressed, and some compounds in a single class have different effects on different receptor types, properties not demonstrated for related compounds in the same class. These are several indicators that reflect the unpredictability of the art.

(5) The relative skill of those in the art:

The relative skill of those working in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance and an example of a clinical trial where normalization of some symptoms associated with metabolic syndrome occured upon administration of candesartan cilexetil or candesartan cilexetil plus feldipine. Diagnostic criteria are identified for the diagnosis of metabolic syndrome.

However, the specification does not provide guidance or examples that would be required to use the method for preventing metabolic syndrome or what criteria would be used to select an individual in need of prevention therapy. Neither have any DNA tests been disclosed that might identify genetic factors of the disease or other diagnostic tests that might be used to identify the individual in need of prevention.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to prevention of metabolic syndrome and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. Claims 11-13 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The use of the genus "metabolically neutral antihypertensive substance" in claim 11 is only partially supported by references to calcium antagonist compounds. Applicant has not provided a written description broad enough to support possession of this genus.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than

those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the

conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a method for the treatment and/or "prevention" of metabolic syndrome, whereby a pharmaceutically and pharmacologically effective amount of an angiotensin II type 1 receptor antagonist, either alone or in combination with a metabolically neutral antihypertensive substance is administered to a subject in need of the treatment or prevention.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is high.

(2) Partial structure:

Some compounds have been given, under the classification of dihydropine calcium antagonists and non-dihydropine calcium antagonists, on pp. 8-9 of the specification. No other classes of compounds or compounds have been given to identify other metabolically neutral antihypertensives.

(3) Physical and/or chemical properties and (4) Functional characteristics:

Calcium receptor antagonists influence the flow of calcium ions into the cells. In general, metabolically neutral antihypertensives are identified as compounds capable of reducing hypertension without influencing the metabolic profile of the subject being treated. Besides the calcium antagonists named, no other physical or chemical properties or functional characteristics have been identified.

(5) Method of making the claimed invention:

Candesartan cilexetil is commercially available. No description of making metabolically neutral antihypertensives is given, although at least some of the calcium antagonists are commercially available.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 11-13 and 17-20 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any metabolically neutral antihypertensives. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of calcium antagonists and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide

adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 11-13 and 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Imura, et al. (US 2003/0187038 A1; priority claim 2000).

Imura teaches the method of the instant claims: administration a fibrogen lowering agent, such as candesartan cilexetil, to rats at concentrations of 1 mg/kg (correspond dose of about 70 mg for a human adult; paragraphs 0210, 0213; claims 6, 18); formulations for administration contain candesartan cilexetil at 30 mg (Tables 1 and 2); the agents of the invention are useful as prophylactic or therapeutic agents for fibrinogen-related diseases of mammals, which includes metabolic disorders, such as Syndrome X (paragraph 0156). When doses of 30 or 70 mg are converted to equivalent (mole) amounts as candesartan, they correspond to 21.6 and 50.5 mg (dose taught x

MW of candesartan / MW candesartan cilixetil; 30 mg x 440.45 g/mol / 610.66 g/mol = 21.6 mg candesartan equivalent).

10. Claims 11-13 and 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Terashita, et al. (US 2006/0069133 A1; priority 12/2002).

Terashita teaches the elements of the claims: a pharmaceutical agent containina a compound having angiotensin II antagonistic activity is useful for the suppression of body weight gain, before reaching or in a patient with obesity (abstract; claims 2-3); the active agents include candesartan cilexetil, which has been prepared in dosages of 5 and 10 mg (paragraphs 0023; claim 13; paragraphs 0161-0162); prevention and treatment of body weight gain is taught and in association with diabetes, hypertension, hyperlipidemia (paragraph 0003); applicable diseases include Syndrome X (paragraph 0115); administration is taught (paragraph 0109). Doses of 5 and 10 mg correspond to 3.6 and 7.2 mg, when calculated as candesartan (converted on a mole basis).

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy P. Thomas whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TPT/
Timothy P. Thomas
Patent Examiner

Ardin H. Marschel 10/3/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER